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# ANNUAL PROGRESS REPORT

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TITLE OF PROJECT: The Addiction Liabilities of Synthetic Substitutes for Codeine.

Objectives: To find a synthetic analgesic and antitussive drug which would be as safe or safer than codeine.

ABSTRACT (OR SUMMARY) OF RESULTS:

a. Since start of project: See annual reports for 1952 through 1960.

b. During the current report period: Testing has been completed or is in progress on the following compounds:

1. Dextro-3-dimethylamino-1,1-diphenylbutyl ethyl sulfone Hcl (ARC I-C-26). This compound was found to have addictiveness greater than codeine and has been dropped from further consideration.

2. Ethyl-1(2-Carbamylethyl)-4-phenylpiperidine-4-carboxylate Hcl (ARC I-D-29). This meperidine congener is effective orally as an antitussive in doses of 50 mg. It induces only a partial spectrum of morphine-like behavioral effects, even in doses of 1000 mg, and will suppress abstinence from morphine only partially. Its addictiveness is less than that of codeine.

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3. 1,2-Dimethyl-3-phenyl-3-propionoxy-pyrrolidine HCl (ARC I-O-1). This meperidine congener, which is reported to be an effective analgesic orally, has less addictiveness than codeine. However toxicity may prevent clinical usage.

4. 2,2-Diphenyl-4(1-[4-(N-piperidine)-4-carboxamide] -piperidine)-butyronitrile (ARC I-D-21). This meperidine congener is an effective analgesic that has been reported not to be addictive in dogs. It is half as potent as morphine in inducing morphine-like behavioral changes when given subcutaneously, it suppresses abstinence effectively, but following substitution (subcutaneously) for morphine for 10 days, or following direct addiction for 25 days, only minor signs of abstinence were detected. This interesting dissociation of effects may be due to low solubility of the compound, with resultant slow absorption after subcutaneous injection and precipitation in tissue. Evaluation of the material orally is incomplete.

5. 1-2'-Hydroxy-2,5,9-trimethyl-6,7 benzomorphan HBr (ARC I-H-2). This compound is a potent analgesic in man. It is as potent as morphine behaviorally but, surprisingly, is relatively ineffective in suppressing abstinence. However the compound did create addiction nearly as intense as that produced by morphine in a short direct addiction experiment. Studies of the compound are continuing.

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6. 1-Hydroxyethoxyethyl-4-phenyl-4-propionyl-piperidine Hcl (ARC I-D-22). This antitussive meperidine congener is an effective antitussive. Definite codeine-like behavioral effects were not observed with doses of 500 mg; 1700-1800 mg daily partially suppressed abstinence from morphine. This compound is less addictive than codeine.

7. 1-Dimethylamino-3-phenylindane Hcl (ARC I-N-1). This compound is the prototype of a new series of analgesics that resemble amphetamine more than morphine. It is analgesic in man, but in our experiments it did not induce morphine-like behavioral change after 200 mg orally, did not suppress abstinence, and did not create addiction.

8. 2-Amino-Indane Hcl (ARC I-N-2). This compound is a more potent agent than I-N-1 (see above). It did not create morphine-like behavioral effects, did not suppress abstinence and did not create addiction.

9. 2'-Hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (ARC II-C-2). This compound is an opiate antagonist that has been reported to be half as effective as morphine as an analgesic in man. It does not cause morphine-like behavioral effects and suppresses abstinence only partially. Direct addiction experiments are in progress, but patients are refusing to continue on the drug because of lack of attractive subjective effect, mental confusion, and irritation of subcutaneous tissues at injection sites.

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10. 1-(p-Chlor-phenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hcl (AEC I-K-1). Testing of this substance was completed during the year and results confirmed those previously described. The compound, though an analgesic clinically, has less addictiveness than codeine and even less than d-propoxyphene. It will come into the market during 1962.

Summary: During the reporting period, testing was completed or in progress on 10 compounds. One of these was dropped because of high addictiveness. Two (I-D-20 and I-D-22) are promising antitussives with little or no addiction liability. Four (I-K-1, I-N-1, I-N-2 and II-C-2) have promise of being analgesics of low addictiveness, and one of these (I-K-1) is coming into the open market. Two (I-D-21 and I-H-2) present interesting dissociations of effect worthy of further investigations.

PLANS FOR FUTURE:

Immediate: Complete testing on I-D-21, I-H-2, I-N-1, I-N-2, and II-C-2. Investigate N-allyl-14-hydroxy-dihydromorphinone and any other compounds recommended by the Committee on Drug Addiction and Narcotics, National Research Council, NAS.

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Long Range: Continue search until the Drug Addiction Committee, NRC, NAS, is satisfied that completely adequate substitutes for codeine are available.

REPORTS AND PUBLICATIONS (during the current report period).

1. Fraser, H.F. and Isbell, H.: Human pharmacology and addictiveness of Ethyl 1-(3-cyano-3,3-phenylpropyl)-4-piperidine carboxylate Hcl (R-1132, Diphenoxylate). Bull Narcotics 13: (1) 29-45, 1961.

2. Fraser, H.F., Martin, W.R., Wolbach, A.B., and Isbell, H.: Addiction liability of an isoquinoline analgesic, 1-(p-Chlorphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Clin. Pharmacol. Therap. 2: (3) 287-299, 1961.

3. Fraser, H.F. and Wolbach, A.: The addiction liability of Alpha-dl-acetoxy-4,4-diphenyl-6-methylaminoheptane Hcl (NIH-7087, ARC I-C-25) and 6-Acetyl-3-ethoxydihydromorphine (NIH-7025, ARC I-A-33). Bull. Drug Addiction and Narcotics, Add. 2, pp 1-3, 23rd Meet., Committee on Drug Addiction and Narcotics, NRC, Washington, D.C. Natl. Acad. Sci., 1961.

4. Fraser, H.F., Essig, C.F. and Wolbach, A.B.: Evaluation of carisoprodol and phenyramidol for addictiveness. Bull. Narcotics 13: (4) 3-7, 1961.

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